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EXAMINER	
TAYLOR, JANELL E	
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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/840,722	Applicant(s) MACLEOD ET AL.	
	Examiner Janell Cleveland Taylor	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,21,23-29,36-75 and 85-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,21,23-29,36-75 and 85-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 7 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

The following is a supplemental Office Action. The initial Office Action, paper #6, mailed July 3, 2002, contained two errors, which were pointed out by Mr. David Parker. The following Office Action rectifies those errors, and resets the response period.

Claim Objections

1. Claim 43 is objected to because of the following informalities: the claim contains several misspelled words: fluorophore is spelled "flurophore" on two occasions, and succinamide is misspelled "succinomido". Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 20, 3-4, 86, 23, 29, 36, 45-77, 87, 21, 24-28, and 37-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 is drawn to a method, but no clear and defined steps are recited in the independent claims. Phrases such as "the DNA molecule having a first linker sequence" are vague and do not set forth a defined method. While minute details are not required in method claims, at least the basic steps must be recited in a *positive, active fashion.* See Ex Parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986.) Furthermore, claim 20 is indefinite for failing to recite a final process step which agrees back with the preamble. The claim is drawn to a method for subjecting a DNA molecule to a synthesis reaction, yet the claims recite only primer sets, no clear, active steps of

synthesizing a DNA molecule. The claims do not set forth the relationship between the primers and the DNA synthesis reaction, and therefore, it is not clear whether the claims are intended to be drawn to. Amendment of the claims to read e.g. actual method steps reciting the synthesis of a DNA molecule would obviate this rejection.

4. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to "non-genomic DNA". However, it is not clear what is meant by this phrase, as non-genomic DNA is a non-descript, undefined term. For instance, is DNA originating from the chloroplasts or mitochondria considered to be non-genomic? Is DNA which has already been amplified considered genomic or non-genomic? Is cDNA considered non-genomic? Appropriate clarification and correction is required.

5. Claims 72-73 and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain the phrase "different species/organism/stages of development/conditions." It is not clear what the conditions, etc, differ from. In other words, there is no comparison between two different cells, since only one cell is specified in the claim. The claim could be reworded to say that DNA derived from two cells or two tissue samples cultured under different conditions (etc.) were compared to each other. Appropriate correction is required.

6. Claims 50-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The claims refer to analysis of the product by "Biostar" and "Luminex" technology. However, these are the names of two specific companies, both of which have multiple technologies and different publications. It is improper to refer to a method simply by the company's name who invented the technology. The method itself must be recited in a clear, and active step. Appropriate correction is required.

7. Claims 50-51 recites the limitation "the Biostar" and "the Luminex" technology. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 87-89 are rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer Manheim Catalog, 1997.

Claims 87-89 are drawn to a primer, and a population of primers, having a 5' sequence for annealing to a linker and a 3' terminal specificity region from 3 to 8 nucleotides in length.

Boehringer Manheim (page 95) teaches random hexamers which may serve as primers. Because these claims do not specifically recite what the sequence of the primers are, any primer which is capable of annealing to a linker and a specificity region

are anticipated. Because these hexamers comprise every sequence, they would have been able to anneal with any nucleic acid. Therefore, the claims are fully anticipated.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 4, 20, 21, 23, 24, 27, 28, 29, 36, 37-42, 44, 45, 48, 57, 58, 59, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (USPN 6,280,949) in view of Kambara et al. (USPN 5,650,274).

12. Claim 20 is drawn to a method of subjecting a DNA molecule to a DNA synthesis reaction, the DNA molecule having a first linker sequence positioned at one end of the DNA molecule and a second linker sequence, different from the first sequence, positioned at the other end of the DNA molecule, wherein said DNA is subjected to a DNA synthesis reaction with a primer set comprising: a) a first primer, wherein the 5' sequence of said primer is complementary to said first linker sequence and the 3' sequence of said primer comprises a specificity region; b) a second primer, wherein the 5' sequence of said primer is complementary to said second linker sequence and the 3' sequence of said primer comprises a specificity region. Claim 4 is drawn to the DNA being cDNA. Claim 45 is drawn to the DNA synthesis reaction being analyzed. Claim 57 is drawn to the analysis of the products being performed on a membrane. Claim 58 is drawn the analysis being performed on a solid matrice. Claim 59 is drawn to the solid

matrice being a DNA chip. Claim 85 is drawn to the first and second primers being employed to amplify the DNA molecule. Claim 21 is drawn to the amplification being performed on an array. Claim 23 is drawn to identifying the amplified DNA. Claim 29 is drawn to the type of amplification reaction. Claim 36 is drawn to a label being incorporated into said amplified DNA. Claim 27 is drawn to the length of the first primer set's specificity region. Claim 28 is drawn to the length of the specificity region of the second primer set. Claim 37 is drawn to the label being incorporated by means of a labeled primer. Claim 38 is drawn to partial nucleotide sequence identification by the identity of the label. Claim 39 is drawn to the label being a chromophore. Claim 40 is drawn to the label being a fluorophore. Claim 41 is drawn to the label being an affinity label. Claim 42 is drawn to the label being a dye. Claim 44 is drawn to various types of dyes, including Texas Red.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

13. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claim 20 above, and further in view of Leushner (USPN 5,830,657).

Claim 3 is drawn to the method of claim 20, wherein said DNA is non-genomic DNA.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated

linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teaches non-genomic DNA.

Leushner teaches DNA synthesis for the purpose of sequencing. Leushner teaches that the DNA to be sequenced may be from a genomic or non-genomic source. (Col. 6, lines 4-6).

It would have been prima facie obvious to combine the art of Lizardi and Kambara with that of Leushner. This is because it would have been obvious to synthesize "non-genomic" DNA. Leushner defines non-genomic DNA as DNA which

has already been amplified. As Leushner points out, this would have been useful for sequencing, as it would have been useful to amplify small amounts of DNA and then sequence it, in order to assure that there was enough product to obtain good results from the sequencing reaction.

14. Claims 46, 71-74, 76, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claim 20 above, and further in view of Black. (USPN 6,310,193).

The claims are drawn to analysis by electrophoresis, and to the DNA being derived from a different species, a different organism, at different stages of development, cultured under different conditions, or comparing normal tissue to diseased tissue.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach DNA derived from the above-mentioned different sources.

Black teaches, "nucleic acids for diagnosis may be obtained from an infected individual's cells and tissues, such as bone, blood, muscle, cartilage, and slin. Genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR or other amplification technique prior to analysis. RNA or cDNA may also be used in the same ways. Using amplification, characterization of the species and strain of prokaryote present in an individual, may be made by an analysis of the genotype of the prokaryote gene. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the genotype of a reference sequence...DNA sequence differences may also be detected by alterations in electrophoretic mobility of the DNA fragments in gels..." (Col. 21 bridging col. 22).

It would have been prima facie obvious to combine the teachings of Lizardi and Kambara with those of Black. This is because it would have been useful to compare the products of the DNA synthesis in order to determine their sequence, or gain valuable information as to mutations, etc. caused by various conditions or existing between various organisms. It would also have been obvious to use gel electrophoresis in analyzing the products, as it would have been a quick and cost-effective method for identifying the products.

15. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi and Kambara as applied to claim 20 above, and further in view of Karger (USPN 4,865,707).

Claim 47 teaches the method of claim 45, wherein said analysis of products is by capillary gel electrophoresis.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5'

terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teaches analysis of products using capillary gel electrophoresis.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use capillary gel electrophoresis with the invention of Lizardi and Kambara. This is because capillary gel electrophoresis would have provided for separation times of less than 30 minutes, permitting trace level determinations of molecular weights, and resulted in extremely high resolution separations. (Abstract of Karger).

16. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claim 45 above, and further in view of Winger (USPN 5,853,990).

Claim 49 is drawn to the analysis of products being by energy transfer.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches

hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach analysis of products by energy transfer.

Winger et al. teaches the use of a reporter and quencher fluorescent dye for use in real-time PCR assays.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi and Kambara with those of Winger. This is because it would have been useful to discriminate between target-contacted probe and target non-contacted probe. Also, it would have allowed for detection of a target DNA sequence in a homogenous, real time system.

17. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claim 45 above, and further in view of Crosby (USPN 6,090,572).

The claim is drawn to the method of claim 45, wherein analysis of the products is by the Biostar technology.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated

linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach the use of BioStar technology in analyzing the products.

Crosby teaches the Biostar technology of a filtration and extraction device and a method for using the device.

It would have been prima facie obvious to combine the teachings of Lizardi and Kambara with those of Crosby. This is because the BioStar method of Crosby teaches a simple, disposable, manual filtration and extraction device. The method provides a

sample directly to an analytical method. This would have allowed for a quick analysis at a relatively low cost.

18. Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claim 45 above, and further in view of Chandler (USPN 6,139,800).

Claim 51 is drawn to the method of claim 45, wherein said analysis of products is by the Luminex technology.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to

the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach the use of Luminex technology in analyzing the products.

Chandler teaches interlaced lasers for multiple fluorescent measurements.

It would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of Lizardi and Kambara with those of Chandler. This is because

the method of Chandler for analyzing samples would have allowed for exciting a sample particle at multiple wavelengths at substantially the same time and/or space domain. Also, it would have allowed for the practitioner to extend the system to a multitude of excitation wavelengths at no substantial cost or effect to measurement accuracy. (Col. 3).

19. Claims 52 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claim 45 above, and further in view of Higuchi (Biotechnology, Vol. 11, NO. 9, Sept. 1993).

The claims are drawn to the analysis of products comprising quantifying amplification, and real-time PCR.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach quantifying amplification.

Higuchi et al. teaches quantitative PCR using real-time amplification. (Abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi and Kambara with those of Higuchi. This is because using real time PCR would have allowed for the rapid analysis of a sample. Furthermore, using quantitative PCR would have allowed the practitioner to know the relative starting amount of the product.

20. Claims 53-54 rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara and further in view of Higuchi, as applied to claim 52 above, and further in view of Rein (USPN 6,316,190).

The claims are drawn to the quantifying being done by measuring the ratio of each product to a co-amplified gene or to a panel of reference genes.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach quantifying amplification.

Higuchi et al. teaches quantitative PCR using real-time amplification. (Abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi and Kambara with those of Higuchi. This is because using real time PCR would have allowed for the rapid analysis of a sample. Furthermore, using quantitative PCR would have allowed the practitioner to know the relative starting amount of the product.

Neither Lizardi, Kambara, nor Higuchi teach the quantifying being done by measuring the ratio of products to a gene or panel of genes.

Rein teaches, "In quantitative PCR, the level of a viral nucleic acid is measured by monitoring PCR amplification products, and comparing the amount of amplified nucleic acid obtained, as compared to an amplification product obtained from amplification performed on a known reference nucleic acid." (Col. 11, 2nd paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi, Kambara, and Higuchi with those of Rein. This is because comparing the quantitative level of the PCR to a reference would have allowed for the relative abundance of the target to be determined and compared. Furthermore, it would have allowed for information to be determined about the target in terms of its quantity.

21. Claims 56 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara as applied to claims 45 and 21 above, and further in view of Duchamel (USPN 6,068,843).

The claims are drawn to the amplification and analysis being performed on a multi-well plate.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence

complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach a multi-well plate, although Lizardi teaches an array for amplification.

Duchamel teaches a multi-well plate for detection of product. (Col. 16, lines 36 and 44-45).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi and Kambara with those of Duchamel. It would have been obvious to amplify the sample and detect it in a multi-well plate. This would have allowed for different areas containing different primers as well as different probes, so that multiple reactions would have taken place at the same time. It would have allowed for the amplification reactions and detections to be done

under substantially the same conditions for all the samples, which would have allowed for an accurate quantitative comparison.

22. Claims 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi in view of Kambara, as applied to claim 20 above, and further in view of Stoler (USPN 5,912,147).

The claims are drawn to the method of claim 20, performed on DNA derived from a normal cell or tissue and on DNA derived from a different cell or tissue (claim 60), and on DNA derived from a cancerous cell or tissue (claim 61).

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a

fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach performing DNA synthesis on both a normal cell or tissue and a cancerous cell or tissue.

Stoler teaches DNA was prepared from tissue samples from patients with sporadic colorectal cancer. Stoler teaches amplifying such samples and comparing the sample to a sample from normal tissue. (Col. 8, lines 14-44).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Lizardi and Kambara with those of Stoler. This is because it would have been obvious to compare samples from a cancerous patient with those of a normal patient. This would have allowed for tumor-specific alterations to be detected and compared with normal cells or tissues. This would have allowed the practitioner to pinpoint the mutations which may have been responsible for the cancerous state.

23. Claims 62-70 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi and Kambara as applied to claim20 above, and further in view of Endege (USPN 6,262,334).

The claims are drawn to the method of claim 20 performed on normal DNA and on DNA derived from a cell or tissue treated with various compounds and biological agents.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection

molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have

then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach comparing a normal cell to one which has been treated with various compounds and agents.

Endege teaches "In yet another aspect, the invention provides pharmaceutical compositions including the subject nucleic acids. In one embodiment, an agent which alters the level of expression in a cell of a nucleic acid which hybridizes under stringent conditions to one of SEQ ID NOS: 1-544 or a sequence complementary thereto is identified by providing a cell, treating a cell with a test agent, determining the level of expression in the cell of a nucleic acid...and comparing the level of expression in the treated cell with the level of expression of the nucleic acid in an untreated cell, wherein the change in the level of expression of the nucleic acid in the untreated cell is indicative of an agent which alters the level of expression of the nucleic acid in a cell.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi and Kambara with those of Endege. That is because it would have been obvious to compare the level of expression of a normal cell with those of a cell treated with an agent. This would have provided information as to the usefulness of certain compounds and agents as pharmaceutical compounds or as methods of treating an individual. This would have

been beneficial in assessing the possible treatment options for a patient with a diseased state.

24. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi and Kambara as applied to claim 23 above, and further in view of Lockhart (USPN 6,329,140).

Claim 25 is drawn to the method of claim 23, wherein said identification is performed by a computer program.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to

the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teach identification by using a computer program.

Lockhart teaches "a hybridization assay between the target molecule and the probes in the array generates data about which probes the target has hybridized to, as well as the extent of hybridization, if the data is so desired. Computer programs are then used to process the data." (Col. 1, bridging col. 2.)

It would have been prima facie obvious to combine the teachings of Lizardi and Kambara with those of Lockhart. This is because it would have been obvious to use a computer program to analyze the results of the amplified DNA. A computer program would have saved time and would have been capable of storing large amounts of data.

25. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi and Kambara as applied to claim 37 above, and further in view of Mathies (USPN 6,177,247) in view of Ward (USPN 5,759,781).

Claim 43 is drawn to the 5' end of the primer comprising an amino moiety and a fluorophore covalently attached by the reaction of succinamide ester.

Lizardi teaches multiple strand displacement amplification of concatenated DNA. The target DNA is concatenated with linkers which are ligated to the target. Primers complementary to the linker are then hybridized to denatured strands of the target/linker complex. (See figure 4 and Col. 5, lines 1-6). Lizardi also teaches detection and quantification of nucleic acids amplified using detection labels, which can be incorporated directly into amplified nucleic acids or can be coupled to detection molecules. Lizardi also teaches Texas Red. (Col. 12). Lizardi also teaches detection using spectrophotometers. (Col. 13). Lizardi also uses solid-state substrates for use in solid-state detectors, including nitrocellulose membranes. Lizardi also teaches arrays. (Col. 15).

Lizardi does not teach that the primers are complementary to the linker sequence at their 5' end and comprises a specificity region at their 3' end.

Kambara et al. teaches digesting a long DNA fragment at a certain sequence portion using an enzyme or the like, and ligating the DNA, which is labeled with a fluorophore or the like, with a DNA oligomer which as a known sequence (the linker) to the digested portion of the DNA fragments. (Col. 2, lines 15-25). Kambara also teaches heating the molecule described above (a target DNA sequence flanked by two ligated linkers on either side) and causing it to become single stranded. Kambara then teaches hybridizing a primer comprising the sequence complementary to the known sequence portion at the terminus and the base sequence complementary to two bases at the 5' terminal of the unknown sequence portion. Kambara teaches that the base sequence complementary to the terminal end of the unknown sequence portion may be from 2-6 bases in length. (Col. 3).

It would have been prima facie obvious to combine the teachings of Lizardi with those of Kambara. This is because it would have been obvious to use primers which hybridized with both the linker region and the target. This would have allowed for DNA sequencing, as the primer sequence would have been known, and would have allowed for the practitioner to know the first 2-6 bases of the target. The practitioner would have then been able to "walk" along the nucleic acid and determine its sequence, using successive primers. Having a portion of the primer which hybridized with the linker would have allowed for stability of the primer and would have provided a reference point with which to gauge the hybridization of the primer.

Neither Lizardi nor Kambara teaches an amino moiety and a fluorophore covalently attached by the reaction of succinamide ester.

Mathies teaches a modified primer which contains an amino modification at the 5' end of the oligomer for attaching a fluorescent molecule. (Col. 10).

Mathies does not teach succinamide ester.

Ward teaches probes with N-succinamide ester coupled to it.

It would have been obvious to combine the teachings of Mathies and Ward. This is because it would have been obvious to attach the succinamide ester of a fluorophore to the amino moiety of a nucleic acid. This would have allowed for a strong attachment which would have been identifiable in the assay.

It also would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Lizardi and Kambara with those of Mathies and Ward. This is because it would have allowed for the attachment of a fluorescent molecule to the primer, which would have allowed for its identification.

Summary

Claims 3-4, 20, 21, 23-28, 29, 36-76, and 85-89 are pending. The claims that were misnumbered in the previous Office Action have been renumbered, and agree with Applicant's numbering as submitted in preliminary amendment of 10/5/01. Claim 43 is objected to. Claims 3-4, 20, 21, 23-28, 29, 36, 37-44, 45-77, 86, and 87 are rejected under 35 U.S.C. 112, second paragraph. Claims 87-89 are rejected under 35 U.S.C. 102(b). Claims 3-4, 20, 21, 23-28, 29, 36-76, and 85-86 are rejected under 35 U.S.C. 103(a). No claim is free of the prior art. No claim is allowable.

Conclusion

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or 872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

September 2, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600